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Type of tobacco and risk of lung cancer: a case-control study from Uruguay

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Summary

During the time period January 1988-December 1989, a case-control study involving 224 cases of lung cancer and 252 controls was carried out at the Instituto de Oncologia, Montevideo, Uruguay, in order to analyze the patterns of risk of lung cancer, associated with smoking blond (flue-cured) and black (air-cured) cigarettes. Mixed smokers carried a significantly higher RR of 3.2, when compared with smokers of blond cigarettes. Lifetime smokers of black cigarettes displayed a non-significant 30% increased risk compared with blond cigarette smokers. Since the differences between mixed and pure black were not significant, and the confidence bounds between both categories were overlapping, the possibility of a chance finding arises. If mixed and lifelong (pure) black tobacco smoking is in fact not different, then ever use of black tobacco is the relevant measure. Ever use of black tobacco was associated with a significant 2-fold increase in the relative risk for all cases and for squamous cell lung cancer. Given the high prevalence of ever use of black tobacco in Uruguay, the attributable fraction for black tobacco smoking in lung cancer could be as high as 29.3 percent.

Introduction

Lung cancer is the leading neoplastic cause of death among Uruguayan males, with an age-adjusted mortality rate of 56.8 for the whole country and an age-adjusted incidence rate

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of 83.3 for 1987 in the capital city of Montevideo [1]. Numerous prospective and retrospective epidemiological studies have confirmed that cigarette smoking is the major cause of lung cancer. Furthermore, the risk of lung cancer increases with all types of tobacco products [2].

Uruguay is characterized by a high proportion of smokers of black tobacco cigarettes. In fact, about 40% of the male population smokes black products. This habit has been consistently shown as a risk factor for esophageal, oropharyngeal, laryngeal and bladder cancers [3–10]. According to chemical analysis, black tobacco contains lower amounts of polycyclic hydrocarbons and higher amounts of *N*-nitroso compounds than blond tobacco [11]. In two previous studies on lung cancer, black tobacco smokers showed an increase in risk of 70%, taking as referents smokers of blond tobacco [12, 13]. Both studies were handicapped by the low proportion of smokers of blond tobacco; in this sense Uruguay appears to be a rather convenient place to address the point, due to the similar proportion of smokers of both kinds of cigarettes. The objective of the present study is to estimate the risk associated with smoking different types of tobacco.

Subjects and Methods

During the time period January 1988 to December 1989, all incident cases of lung cancer admitted for diagnosis and/or treatment to the Cancer Institute of Montevideo, Uruguay, were selected for this study. In total, there were 235 cases occurring in men and 17 in women. The study was restricted to males because of the small number of females. Nine cases were unable to complete the questionnaire, due to advanced disease. One further case was excluded due to a diagnosis of rhabdomyosarcoma. Since the study was designed in order to estimate the risk of the type of tobacco, the only non smoker case was excluded from the study, leading to a final total of 224 cases. Of these cases, 197 had histologic diagnosis of lung carcinoma. Squamous cell carcinomas comprised the largest group (98 cases), followed by adenocarcinoma (41 cases) and small cell cancers (33 cases). Twenty-seven cases with clinical, radiologic and endoscopic evidence of lung cancer were also included in the analysis. In the same period, 793 male patients afflicted with other cancers or non-neoplastic conditions, were also admitted to the Institute of Oncology. From this potential source of controls, 86 were excluded due to terminal illness, 366 due to a diagnosis of tobacco-related cancer, 43 with uncertain primary site, and 46 non-smokers. As a final result, 252 patients with a variety of disorders were used as controls. Both cases and controls were interviewed by 3 trained social workers, unaware of the hypothesis to be tested and of any previous exposure. The questionnaire included, among other variables, information concerning demographic variables, social class, occupation, and a complete tobacco history, and was administered to all patients shortly after admission.

The type of tobacco smoked was classified as blond or black, according to the commercial brands registered in all questionnaires. The category 'mixed' was used to designate those smokers which used both blond and black tobacco, either synchronically or metachronically. In a later stage of the analysis, lifelong (pure) blond tobacco smokers were compared with ever smokers of black tobacco (mixed plus pure black).

TABLE 1
Distribution of cases by histologic type

Type	Frequency	Percent
Squamous cell	98	43.8
Small cell	33	14.7
Adenocarcinoma	41	18.3
Large cell	11	4.9
Unclassified	14	6.2
Clinical diagnosis	27	12.1
Total	224	100.0

Data analysis

Univariate estimates of relative risk, approximated by the odds ratio, were obtained by exponentiating the coefficient of each variable. Since the study followed an unmatched design, unconditional logistic regression was used in order to obtain multivariate estimates for each study variable. Different models were fitted, using the adjusting variables as categorical or continuous. The final models included categorical variables. All estimations were performed using the program GLIM [14].

Results

In Table 1, the distribution of cases by histologic type is shown. In accordance with most series of western countries, squamous cell carcinoma was the most frequent type (43.8%), followed by small cell carcinoma and adenocarcinoma.

TABLE 2
Distribution of controls by diagnosis

ICD-9	Site	*N*	%
173	Skin cancer	70	27.8
185	Prostatic cancer	38	15.1
200-8	Lymphoma-leukemia	29	11.5
153-4	Colorectal cancer	29	11.5
–[a]	Non-neoplastic diseases	27	10.7
–[b]	Other malignant tumors	16	6.2
187	Cancer of the penis	12	4.8
151	Gastric cancer	12	4.8
186	Cancer of the testis	6	2.4
171	Sarcomas	6	2.4
191	Central nervous system	5	2.0
210-4	Benign tumors	2	0.8
–	Total	252	100.0

[a]Diseases of the eye, hernia, osteoarticular disorder.
[b]Melanoma, parotid, gallbladder, and thyroid cancer.

TABLE 3
Distribution of cases and controls by sociodemographic factors

Variable	Cases		Controls	
	No.	%	No.	%
Age (years)				
≤ 54	57	25.5	63	25.0
55–64	69	30.8	58	23.0
65–74	65	29.0	78	31.0
75+	33	14.7	53	21.0
County				
Montevideo	102	45.5	106	42.1
Other	122	54.5	146	57.9
Residence				
Urban	156	69.6	178	70.6
Rural	68	30.4	74	29.4
Education (years)				
0–3	64	28.6	83	32.9
4+	160	71.4	169	67.1
Monthly income (dollars)				
≤63	155	69.2	170	67.5
64+	69	30.8	82	32.5
No. of patients	224		252	

In Table 2, the distribution of controls by ICD-9 rubric is shown. Only 27 patients (10.7%) were afflicted by non-neoplastic diseases. Among the cancer sites, skin cancer was the most frequent, followed by prostatic cancer, leukemias and lymphomas.

TABLE 4
Relative risks of lung cancer for intensity, cessation, and duration of smoking

Variable	Category	Cases/controls	RR	95% CL
Amount[a] (cig/day)	1–10	21/78	1.0	–
	11–20	61/89	2.0	1.1–3.7
	21–30	53/35	4.2	2.1–8.5
	31+	89/50	5.1	2.7–9.7
Chi-squared= 32.7		$P<0.001$		
Duration[b] (years)	1–29	28/78	1.0	–
	30–39	34/46	1.9	0.9–4.0
	40–49	70/48	5.6	2.7–11.5
	50+	92/80	7.1	3.1–16.2
Chi-squared= 29.2		$P<0.001$		
Years since quit[b]	Current smokers	177/144	1.0	–
	1–4	21/18	1.0	0.5–2.0
	5–9	14/15	0.9	0.4–2.2
	10+	12/75	0.1	0.0–0.2
Chi-squared= 43.3		$P<0.001$		

[a]Adjusted for age, county, education, income, smoking duration, filter use and type of tobacco.
[b]Adjusted for age, county, education, income, amount smoked, filter use and type of tobacco.

TABLE 5
Relative risks of lung cancer for type of tobacco and other smoking variables

Variable	Category	Cases/controls	RR	95% CL
Type of tobacco[a]	Pure blond	56/112	1.0	–
	Mixed	71/50	2.8	1.6–4.9
	Pure black	97/90	1.3	0.8–2.3
Chi-squared= 1.3		P=0.25		
Type of tobacco[a]	Pure blond	56/112	1.0	–
	Ever black	168/140	1.9	1.2–2.9
Filter use[b]	No	156/150	1.0	–
	Yes	68/102	0.4	0.2–0.7
Hand rolling[a]	No	40/79	1.0	–
	Yes	184/173	1.6	0.9–2.9

[a]Adjusted for age, county, urban/rural condition, education, income, smoking duration, smoking amount, cessation, and filter use.
[b]Adjusted for age, county, education, income, smoking duration, amount and type of tobacco.

Aside that controls were slightly older than cases, the distribution by residence, urban/rural condition, education and income was very similar for both cases and controls (Table 3). Intensity of smoking, measured in lifetime average consumption of cigarettes per day, showed a strong dose-response pattern with a RR of 5.1 for heavy smokers (Table 4). Also, smoking duration displayed a monotonic gradient of increasing risks, with a highly significant test for linear trend. Interestingly, smoking cessation was associated with a reduction in risk of 90% after 10 years since stopping, but showed a sustained risk before this time.

In Table 5, the effect of the type of tobacco smoked is shown, taking as the referent category smokers of blond tobacco. The highest risk was carried by mixed smokers (RR=2.8). Concerning pure black tobacco smokers, there was a 30% increase in risk, which was non significant. Ever smokers of black tobacco showed a significant increase in risk of 1.9, compared with lifelong smokers of blond tobacco. The use of filter cigarettes was associated with a significant reduction in risk of 60%, and smokers of hand-rolled cigarettes showed an RR of 1.6. The effect of the type of tobacco was further explored by histologic type of lung cancer (Table 6).

TABLE 6
Relative risks of lung cancer for ever smokers of black tobacco. Referent category: lifetime smokers of blond tobacco[a]

Cell type	No. cases	RR	95% CL
Squamous cell	98	2.75	1.46–5.18
Small cell	33	2.03	0.67–6.08
Adenocarcinoma	41	1.75	0.76–4.07
Other types	25	2.73	0.82–9.12
No morphology	27	1.05	0.37–2.94
All cases	224	1.88	1.18–2.99
All cases with histology	197	2.12	1.29–3.46

[a]Adjusted for age, residence, urban/rural condition, education, income, amount smoked, smoking duration, years since quit, and filter use.

Ever smokers of black tobacco showed increased relative risks for squamous cell, small cell and large cell carcinomas. Adenocarcinoma displayed a moderate increase in risk, whereas cases without histologic verification displayed no effect of black tobacco.

Discussion

The present study replicates the previous findings concerning main tobacco variables, like smoking amount and duration [15, 16]. Regarding the type of tobacco, mixed smokers showed the highest risk, whereas smokers of black tobacco displayed a slightly elevated relative risk of 1.3. This pattern of risks for different types of toabcco smoking, showing a greater effect for mixed smokers could have resulted from bias or a chance finding. Concerning bias, the similar distribution of cases and controls according to socio-demographic variables makes unlikely the existence of selection bias. It is conceivable that patients afflicted by lung cancer might be more concerned about their past smoking habits, giving therefore a more precise response to the questionnaire. This could have resulted in a higher proportion of mixed smokers among cases. Although this possibility cannot be excluded, the fact that almost 90% of the controls were cancer controls, suggests a similar recall [17]. In order to exclude interviewer bias, we performed separate analysis for each interviewer, and the results were very similar. The possibility of residual confounding is an unlikely explanation for the high risk associated with smoking both types of tobacco, since this variable was fully controlled for age, residence, education, income, amount smoked, duration, years since quit, and filter use. Since our study examined only tobacco variables, it is not possible to exclude confounding due to other risk factors for lung cancer like occupation and diet. Nevertheless, the strength of the association makes this possibility unlikely.

In order to exclude a chance finding, we also recalculated the relative risk of mixed smokers taking as referents black tobacco smokers. This resulted in a non-significant increase of the relative risk for mixed smokers, with overlapping confidence bounds (RR=1.84 CI=0.97–3.49). Thus, this estimation supports the possibility of a chance finding. On the other hand, the existence of a real effect for mixed smokers cannot be excluded. A recent study on oesophageal cancer, conducted in Thailand, showed a relative risk 1.7 times higher for mixed smokers, compared with pure black tobacco smokers (F.X. Bosch, personal communication). If the difference between mixed and black tobacco smokers is merely due to random variation, then ever smoking black tobacco is the relevant measure, and the significant increase in risk associated with this more crude measure of black products use, could have important epidemiologic implications. Assuming that almost 45% of the Uruguayan population ever smoked air-cured cigarettes, the crude attributable risk could be as high as 29.3%. Of course, this finding needs further elaboration and replication from forthcoming studies. Concerning the mechanisms of action, a more powerful role of black tobacco in early stages of carcinogenesis has been suggested [10]. This could be related with the higher levels of tobacco-specific *N*-nitroso compounds with organ-specific lung activity in black tobacco.

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